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# Moderators, Mediators, and Other Predictors of Risperidone Response in Children with Autistic Disorder and Irritability

**L. Eugene Arnold, M.D., Department of Psychiatry, Ohio State University, Columbus, Ohio, The Nisonger Center, Ohio State University, Columbus, Ohio, Cristan Farmer, M.A., The Nisonger Center, Ohio State University, Columbus, Ohio, Helena Chmura Kraemer, Ph.D., Department of Psychiatry and Behavioral Sciences (Emerita), Stanford University, Palo Alton, California; Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, Mark Davies, M.P.H., Indiana University, Indianapolis, Indiana, Andrea Witwer, M.A., The Nisonger Center, Ohio State University, Columbus, Ohio, Shirley Chuang, M.S., San Francisco, California, Robert DiSilvestro, Ph.D., Department of Human Nutrition, Ohio State University, Columbus, Ohio, Christopher J. McDougle, M.D., Department of Psychiatry, Indiana University, Indianapolis, Indiana, James McCracken, M.D., Department of Psychiatry and Behavioral Sciences, University of California Semel Institute, Los Angeles, California, Benedetto Vitiello, M.D., Child and Adolescent Treatment and Preventive Intervention Research Branch, National Institute of Mental Health, Rockville, Maryland, Michael G. Aman, Ph.D., The Nisonger Center, Ohio State University, Columbus, Ohio, Lawrence Scahill, Ph.D., Yale Child Study Center, Yale University, New Haven, Connecticut, David J. Posey, M.D., Department of Psychiatry, Indiana University, Indianapolis, Indiana, and Naomi B. Swiezy, Ph.D. Department of Psychiatry, Indiana University, Indianapolis, Indiana**

Abstract

Objective/Background:

The National Institute of Mental Health (NIMH) Research Units on Pediatric Psychopharmacology (RUPP) Autism Network found an effect size of d = 1.2 in favor of risperidone on the main outcome measure in an 8-week double-blind, placebo-controlled trial for irritabilityin autistic disorder. This paper explores moderators and mediators of this effect.

Method:

Intention-to-treat (ITT) analyses were conducted with suspected moderators and mediators entered into the regression equations. MacArthur Foundation Network subgroup guidelines were followed in the evaluation of the results.

Results:

Only baseline severity moderated treatment response: Higher severity showed greater improvement for risperidone but not for placebo. Weight gain mediated treatment response negatively: Those who gained more weight improved less with risperidone and more with placebo. Compliance correlated with outcome for risperidone but not placebo. Higher dose correlated with worse outcome for placebo, but not risperidone. Of nonspecific predictors, parent education, family income, and low baseline prolactin positively predicted

outcome; anxiety, bipolar symptoms, oppositional-defiant symptoms, stereotypy, and hyperactivity negatively predicted outcome. Risperidone moderated the effect of change in 5'-nucleotidase, a marker of zinc status, for which decrease was associated with improvement only with risperidone, not with placebo.

Conclusion:

The benefit–risk ratio of risperidone is better with greater symptom severity. Risperidone can be individually titrated to optimal dosage for excellent response in the majority of children. Weight gain is not necessary for risperidone benefit and may even detract from it. Socioeconomic advantage, low prolactin, and absence of co-morbid problems non-specifically predict better outcome. Mineral interactions with risperidone deserve further study.

## Introduction

The National Institute of Mental Health (NIMH) Research Units on Pediatric Psychopharmacology (RUPP) Autism Network reported the intention-to-treat (ITT) analyses of an 8-week, double-blind, placebo-controlled trial of risperidone for irritability (aggression, self-injury, and severe tantrums) in autistic disorder (autism) (RUPP Autism Network 2002). The effect size d was 1.2 in favor of risperidone on the main outcome measure, the Irritability subscale of the Aberrant Behavior Checklist (ABC) (Aman et al. 1985). This paper explores possible moderators, mediators, and other predictors of that effect.

Moderators can be patient, family, or other contextual characteristics that predict the differential effects of treatment choice and thus suggest a way to match patients to treatments. The seminal Baron and Kenny (1986) guidelines for defining moderators specified only that an interaction between the suspected moderator and independent variable (in this case, treatment) occur. However, the MacArthur Foundation Network subgroup (Kraemer et al. 2002; Kraemer et al. 2008) introduced widely accepted modifications to this definition. The MacArthur guidelines state that to be considered a moderator, a variable must: (1) Have temporal precedence, (2) be independent from treatment, and (3) interact significantly with treatment in the model of analysis. These more stringent guidelines were adopted here as requirements for moderation.

A mediator is a postrandomization variable that is associated with treatment and may help to explain the mechanism through which the independent variable is affecting the dependent variable. Theoretically, the treatment variable affects the mediator, which, in turn, affects the outcome variable (Holmbeck 1997). Given a factorial model, the MacArthur guidelines for mediation require: (1) The temporal precedence of treatment, (2) an association between the mediator and treatment (in this case, point-biserial correlation), and (3) a main effect of the mediator or an interaction between the mediator and treatment. Although this definition does not require a significant effect of treatment on outcome, the absence of such treatment effect would be unusual if the definition is met.

Moderator and mediator analyses in this paper were mainly exploratory, with few a priori hypotheses. However, we did expect that better treatment compliance (measured via tablet count and medication diary) and dose would be related to the effectiveness of risperidone.

## Methods

The design, assessment and ITT results of the RUPP Autism Network risperidone study have been detailed elsewhere

| Moderator | n[a] | Mean (SD) | Range | Median Cut Point |
|---|---|---|---|---|
| Age (in years) | 101 | 8.8 (2.7) | 5.1–16.9 | 8.2 |
| Sex | 101 | 1.2 (0.4) | M–F | |

| | | | | |
|---|---|---|---|---|
| IQ | 91 | 48.4 (24.4) | 9–111 | 48 |
| Income | 99 | 4.4 (2.2) | 1–7 | $50K |
| Parent Education Level | 101 | | | College degree/not |
| Ethnicity | 101 | | | Caucasian/not |
| ADI-R | | | | |
| Social Impairment | 101 | 26.2 (3.4) | 14–33 | 27 |
| Communication impairment | 101 | 17.3 (17.0) | 7–25 | 17 |
| Stereotypy | 100 | 7.8 (2.7) | 1–12 | 8 |
| CY-BOCS | 97 | 15.3 (3.4) | 3–20 | 16 |
| ABC (BL) | | | | |
| Irritability | 101 | 25.8 (7.3) | 3–44[b] | 25 |
| Stereotypic behaviors | 101 | 9.8 (4.7) | 1–21 | 10 |
| Hyperactivity | 100 | 32.1 (9.0) | 11–48 | 33 |
| CGI Severity | 101 | 5.1 (0.70) | 4–7 | 5 |
| CSI (BL) | | | | |
| Inattention | 101 | 17.1 (6.0) | 1–27 | 18 |
| Hyperactivity | 101 | 16.7 (6.1) | 2–27 | 17 |
| Conduct | 101 | 4.3 (4.5) | 0–16 | 3 |
| Oppositional | 101 | 10.0 (5.6) | 1–22 | 10 |
| Enuresis | 101 | 1.9 (2.1) | 0–6 | 1 |
| Encopresis | 101 | 0.8 (1.1) | 0–3 | 0 |
| Anxiety | 101 | 14.4 (8.0) | 0–42 | 13 |
| Anorexia | 98 | 0.8 (1.6) | 0–7 | 0 |
| Bulimia | 99 | 1.1 (1.7) | 0–9 | 0 |
| Depression | 97 | 3.1 (4.0) | 0–24 | 2 |
| Bipolar disorder | 98 | 7.3 (5.9) | 0–24 | 6 |
| Leptin (ng/mL) | 100 | 5.6 (5.7) | 1.0–36.7 | 3.4 |
| Prolactin (ng/mL) | 95 | 10.2 (8.90) | 2.3–39.6 | 6 |
| Weight (kg) | 96 | 35.2 (18.7) | 16.1–35.2 | 30 |
| Ferritin (ng/mL) | 60 | 25.0 (21.6) | 0.5–116.8 | 20.9 |
| Ceruloplasmin (U/L) | 55 | 162.3 (82.7) | 34.0–393.0 | 150.0 |
| CeruloplasminRID (mg/L) | 57 | 334.0 (157.3) | 97.0–875.0 | 328.0 |
| Serum zinc (μg/dL) | 60 | 162.7 (58.1) | 48.1–291.9 | 164.5 |
| Copper ( μg/dL) | 56 | 81.8 (18.6) | 36.8–116.3 | 85.7 |
| 5'-Nucleotidase (U/L) | 49 | 5.9 (1.3) | 3.7–9.2 | 5.8 |

| | | | | |
|---|---|---|---|---|
| Serum Iron (µg/dL) | 39 | 108.0 (73.7) | 15.0–390.0 | 95.0 |

[a]*n*=101.

[b]Includes an outlier who entered the study by mistake. The range was otherwise 18–44.

*Abbreviations:* IQ=Intelligence quotient; ADI-R=Autism Diagnostic Interview–Revised; CYBOCS=Children's Yale-Brown Obsessive Compulsive Scale; ABC=Aberrant Behavior Checklist; CGI=Clinical Global Impressions; CSI=Child Symptom Inventory; BL= baseline; RID = radial immunodiffusion.

**Table 1.** Potential Moderators of Response to Risperidone

(McDougle et al. 2000; Arnold et al. 2000; Scahill et al. 2001; RUPP Autism Network 2002). Briefly, it was a double-blind comparison of risperidone (n=49) versus placebo (n=52) for 8 weeks, with a weight-based, flexible clinical drug titration for the first 4 weeks. Participants were children and adolescents ages 5–17 (mean 8.8 years) with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 1994) autistic disorder and severe irritability. Primary ITT analyses showed highly significant effects of risperidone on both of the primary outcome measures: The ABC Irritability subscale (57% decrease vs. 14% decrease) and the Clinical Global Impressions– Improvement (CGI-I) (75.5% vs. 11.5% with CGI-I less than 3). The effect size (Cohen d) on the ABC Irritability subscale was 1.2 at 8 weeks.

Using the primary outcome measure of the ABC Irritability subscale score, we explored the effects of possible moderators and mediators. Casting a wide net, we included demographic characteristics, diagnostic measures, symptom severity, and exploratory laboratory analyses (prolactin, leptin, and mineral assays). Mineral assays were included because of reports of mineral abnormalities in autism, especially zinc and copper and their ratio (Faber et al. 2009) and such related proteins as ferritin and ceruloplasmin (Chauhan et al. 2004) and because prolactin, known to be increased by risperidone, has been suspected of increasing ceruloplasmin (DiSilvestro 1986). First, potential moderators (Table 1) and mediators (Table 2) were entered into respective correlation matrices to check for collinearity. By predetermination, any correlation of 0.5 or stronger would result in combining the variables or discarding one. Most correlations were well below 0.2 and nonsignificant. The exceptions were parental education and income, which were correlated with each other ($r=0.40$, $p < 0.0001$), and the Autism Diagnostic Interview–Revised (ADI-R) (Lord et al. 1994) Stereotypy subscale, which correlated both with the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al. 1997) at 0.22 ($p < 0.03$) and with the ADI-R Communication Impairment subscale at 0.27 ( $p < 0.01$). Because all correlations were below $r = 0.5$, all variables were considered in the analysis.

The suspected moderators and mediators were centered according to the guidelines recommended by Kraemer and Blasey (2004). The ordinal moderators were centered around their respective medians, while the binary moderators (and treatment group) were set to —0.5 or 0.5. As change scores, mediators were all considered to be deviations from zero. Centering the data allows the effects to be evaluated at the level of the independent variable that is representative of the group and helps to diminish the effects of multicollinearity (Kraemer and Blasey 2004).

Some variables presented with special considerations for data analysis. For potential mediators, change scores were calculated as percent change (absolute change divided by baseline value) for ease of comparison. For medication-related variables, dose and compliance, different methods were used. Dose, considered to be the prescribed dosage of risperidone, was to be maintained during the final 4 weeks of treatment at the child's optimal dose. This optimal dose was analyzed as both absolute mg/day and mg/kg per day. Compliance was 100% less the percent of

noncompliance, which was calculated as the excess number of tablets returned beyond what should have been returned if all doses were taken, divided by the number that should have been taken. In 31 instances of missing tablet returns, the medication diary kept by the parent was consulted to determine missed doses. Both tablet count and diary reports were converted to percents of missed versus prescribed tablets/doses, and compliance was reported as 100% less this value. The percents determined by the two methods had about the same distribution, and where tablet count was not available, the diary report was used.

With each of these potential moderators and mediators, we reran the original ITT analysis of the primary dimensional outcome variable, the ABC Irritability subscale score, with the suspected moderator or mediator entered into the model. Where possible, variables were used in continuous form for more power in the test of significance (exceptions included gender, education level, and ethnicity), but dichotomous splits were made for visual examination (see Tables 1 and 2 for split points). Because of randomization, all suspected moderators were independent from and temporally preceded the randomly assigned treatment, so the remaining criterion was a significant three-way interaction of moderator, treatment, and time. Suspected mediators all followed treatment. Therefore, the criteria of a significant association between mediator and treatment (judged by point-biserial correlation) and significant three-way interaction of mediator, treatment, and time or a main effect of the mediator were used for mediation effects. For

| | *Placebo* | | | | *Risperidone* | | | |
|---|---|---|---|---|---|---|---|---|
| *Potential mediator* | n[a] | *Mean (SD)* | *Range* | *Median* | n | *Mean (SD)* | *Range* | *Median* |
| Dose | 51 | 2.4 (0.4) | 0.6–2.4 | 1.7 | 49 | 1.7 (0.4) | 0.4–2.3 | 1.3 |
| % Compliance | 51 | 93.6 (15.0) | 6.0–100.0 | 99.0 | 49 | 98.5 (1.80) | 93.0–100.0 | 99.0 |
| | | *% Change*[b] | | | | *% Change*[b] | | |
| Weight change (kg) | 50 | 2.0 (4.0) | −9.0–11.0 | 2.0 | 49 | 11.0 (10.0) | −5.0–38.0 | 10.0 |
| Leptin change (ng/mL) | 40 | 35.0 (55.0) | −34.0–187.0 | 22.0 | 41 | 88.0 (125.0) | −36.0–669.0 | 71.0 |
| Prolactin change (ng/mL) | 33 | 24.0 (79.0) | −70.0–265.0 | 5.0 | 41 | 470.0 (360.0) | −58.0–1508.0 | 413.0 |
| Ferritin (ng/ml) change | 15 | −12.0 (52.0) | −73.0–106.0 | −21.0 | 20 | −2.0 (78.0) | −80.0–296.0 | −19.0 |
| Ceruloplasmin (U/L) change | 13 | −3.0 (49.0) | −89.0–88.0 | −7.6 | 19 | −6.0 (53.0) | −79.0–154.0 | −9.0 |
| CeruloplasminRID (mg/L) change | 16 | −0.5 (35.0) | −42.0–73.0 | −11.0 | 17 | −0.6 (44.0) | −60.0–73.0 | 0.0 |
| Serum zinc (μg/dL) change | 14 | −10.0 (26.0) | −66.0–45.0 | −10.0 | 19 | −7.0 (22.0) | −45.0–35.0 | −8.0 |
| Serum copper (μg/dL) change | 15 | −3.6 (19.0) | −42.0–23.0 | −1.4 | 18 | 3.7 (15.0) | −25.0–28.0 | 5.7 |
| 5′-Nucleotidase (U/L) change | 10 | −5.0 (21.0) | −42.0–22.0 | −2.0 | 13 | 2.0 (16.0) | −26.0–32.0 | 3.4 |
| Serum iron (μg/dL) change | 5 | 89.0 (251.0) | −46.0–533.0 | −38.0 | 10 | 11.0 (125.0) | −61.0–360.0 | 25.0 |

[a]$N = 101$.

[b]Percent change reflects the difference between endpoint (week 8) and baseline values divided by baseline values.

**Table 2.** Potential Mediators of Response to Risperidone